REMARKS

Applicants respectfully request reconsideration and allowance of this application in view of the amendments above and the following comments.

Claims 17-19, 24, 25, 28-30, 32-41, 43-46, 48 and 53-56 were rejected under 35 USC § 112, first paragraph, as failing to comply with the written description requirement. In response, Applicants respectfully submit that the rejected claims do, in fact, comply with the written description requirement. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

a) Claim 17

With respect to claim 17, the Examiner completely misconstrues Applicants' previous arguments. According to the Examiner:

> ***"Applicants argue*** support for the promoter that is 'heterologous to the Rosa26 promoter' ***can be found in claim 31.*** Applicants' argument is not persuasive. Claim 31 was rejected in the last office action as being new matter. Support for such promoters cannot be found. [Emphasis added.]"

Respectfully, Applicants made no such argument. Instead, towards the bottom of page 8 of the amendment filed June 30, 2009, Applicants argued:

> "With respect to claim 31, Applicants point out that the substance of this claim has been brought into main claim 17 and, accordingly, claim 31 has been canceled. However, Applicants further point out that ***support for the feature "heterologous***

> ***relative to the Rosa26 locus" can be found in the original specification at page 8, lines 1-2.*** There is *ipsis verbis* support for the language in the original specification and, thus, clearly no new matter. [Unbolded italics in original and bold italics added.]"

Clearly, support for "heterologous relative to the Rosa26 locus" was urged based on the specification at page 8, lines 1-2, ***not*** claim 31. The specification at page 8, lines 1-3, reads as follows:

> "The promoter of the gene expression cassette ***(which is a heterologous promoter relative to the Rosa26 locus)*** preferably is a ubiquitous or tissue specific promoter, either constitutive or inducible. [Again, emphasis added.]"

There is *ipsis verbis* support in the original specification for "heterologous relative to the Rosa26 locus." Consequently, claim 17 does not, in fact, introduce any new matter.

In the last sentence of the third paragraph on page 3 of the Office Action, the Examiner also misconstrues the wording "said functional DNA sequence." Clearly, this is not a definition of the promoter, as the Examiner implies, but, rather, as the wording of claim 17 clearly states, a further option of the functional DNA sequence introduced into the Rosa26 gene. In order to make this perfectly clear, claim 17 is amended above to separate the functional DNA sequence clause into alternatives (a) and (b). The new language is supported by clause (2) at the bottom of page 4 of the original specification.

b) Claims 53-56

With respect to claims 53-55, Applicants again point out that original claim 16, consistent with the specification at the top of page 5, under point (9), provided for the:

> "Use of the eukaryotic cell of claim 11, the transgenic multi-cell organism of claim 15, or the transgenic non-human mammal of claim 15 for gene function studies, drug development, as disease model animals, etc."

Thus, there is support in the original specification for use of "a biological entity selected from a eukaryotic cell, a transgenic multi-cell non-human organism, or a transgenic non-human mammal obtainable utilizing the method of claim 17" for these purposes.

Claim 53 is directed to the use of such biological entity for studying gene functions.

Claim 54 is directed to the use of such biological entity for drug development, i.e., developing a drug.

Claim 55 is directed to the use of such biological entity in an animal model.

The remainder of each of these claims is simply a recitation of the necessary steps that would be readily apparent to anyone of ordinary skill in the art for performing such use. A specification need not teach well known necessary steps for carrying out a use specifically identified in the specification. Indeed, as stated by the Court in *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), "a patent need *not* teach, *and preferably omits,* what is well known in the art (emphasis added)."

The Examiner says he cannot find a recitation of the specific steps in the original specification. However, he does not respond to Applicants' legal argument repeated above. The specification discloses the intended uses, and, as noted above, claims 53-55 recite the necessary steps that would be readily apparent to anyone of ordinary skill in the art for performing such uses. Accordingly, these necessary steps are implicitly in the specification as filed and may be

claimed. *See, e.g., In re Anderson,* 176 USPQ 331, 336 (CCPA 1973), for the proposition that in determining whether an amendment to a claim constitutes new matter, the question is not whether the added word is a word that is used in the application as filed, but whether the concept embodied by the added word is present in the original specification. The concept embodied by these steps is in the specification as filed in the form of the stated intended uses. Once these intended uses were stated, persons skilled in the art immediately knew these necessary steps for performing such intended uses. Consequently, the concept of these steps is present in the original specification in the form of the intended uses themselves, and adding these steps to the claims does not introduce new matter.

With respect to claim 56, the structure recited is supported, for example, by the paragraph bridging pages 9-10 of the specification. The Examiner says he cannot find support for step (b), but Applicants respectfully submit that the last line of (a1) and all of (a2) at the bottom of page 9 of the specification support step (b). Those portions read as follows:

> "introducing ***into the therewith obtained cell***
>
> (a2) ***a donor DNA comprising the same two mutually incompatible first RRSs*** contained in the acceptor DNA by ***utilizing a recombination vector*** as defined above (emphasis added)."

Clearly, this portion of the specification describes what is claimed in step (b), i.e., using a recombination vector to introduce a functional DNA sequence comprising a donor DNA flanked by two mutually incompatible first RRSs into the cell modified with acceptor DNA in step (a1).

Respectfully, Applicants do not believe that any of the rejected claims contain new matter. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw this rejection. An early notice that this rejection has been reconsidered and withdrawn is earnestly solicited.

Claims 17-19, 24, 25, 28-30, 32-41, 43-46, 48 and 53-56 were rejected under 35 USC § 112, second paragraph, as being indefinite. In response, Applicants respectfully submit that the rejected claims are definite. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw this rejection as well.

With respect to claim 17, Applicants have adopted the Examiner's helpful suggestion and replaced "locus" with "gene."

With respect to claim 19, Applicants respectfully submit that there is no indefiniteness as the terms "site specific recombinase" and "mediated recombination" were well known to persons skilled in the art at the time of filing. Site-specific recombination, also known as conservative site-specific recombination, is a type of genetic recombination in which DNA strand exchange takes place between segments possessing only a limited degree of sequence homology. Site-specific recombinases perform rearrangements of DNA segments by recognizing and binding to short DNA sequences (sites), at which they cleave the DNA backbone, exchange the two DNA helices involved and rejoin the DNA strands (see, N. L. Craig et al., "The mechanism of conservative site-specific recombination," *Annu Rev Genet. 22:* 77-105 (1988), a copy of which is cited on the accompanying information disclosure statement.

With respect to claim 28, Applicants respectfully submit that there is no indefiniteness as the term "primary cell" was likewise well known in the art at the time the present application was

filed. According to the standard textbook "Molecular Biology of the Cell" published by Watson et al. (1988) (ISBN: 0-8053-9614-4), the term is defined as follows: "Although there were repeated efforts to grow cultures from dissociated cells, successes were very infrequent until small amounts of the proteolytic enzyme trypsin were used to dissociate tissue masses into their component individual cells. The dissociated cells (primary cells) usually grew well when seeded onto culture plates at high density." (chapter 25, p. 963). "Primary cultures consist of cells freshly removed from an animal and placed in a dish with cell culture medium" (chapter 24, p. 902).

With respect to claim 30, Applicants respectfully submit that there is no indefiniteness as the term "pharmaceutically active" was likewise well known in the art at the time of filing and, therefore, persons skilled in the art has a clear understanding of when a protein or peptide is considered to be pharmaceutically active. In support, Applicants draw the Examiner's attention, for example, to WO 00/47234 and EP-A-1057891.

With respect to claim 32, Applicants respectfully submit that there is no indefiniteness as the terms "an inducible ubiquitous promoter" and "an inducible tissue specific promoter" refer to an inducible promoter that can be activated in multiple tissues of a multicellular organism. In the context of conditional transgene expression, the inducible, ubiquitous Mx1 gene promoter is described by Kühn et al., *Science, 269:* 1427-1429 (1995), a copy of which is included on the accompanying information disclosure statement. Also, please see the first paragraph on page 8 of the specification, wherein numerous promoters are mentioned along with literature references that provide more details.

With respect to claim 33, Applicants renew their position that the promoters in claim 33 were well known in the art at the time the present application was filed. For example, a list of inducible, ubiquitous promoter used for the expression of Cre recombinase in transgenic animals are shown in Torres & Kühn, 1997, *Laboratory Protocols for Conditional Gene Targeting,* Oxford University Press, USA; ISBN-10: 019963677X, ISBN-13: 978-0199636778; Table 1, a copy of which is also included on the accompanying information disclosure statement.

With respect to claim 35, Applicants have limited claim 35 to dependence on claim 18, and added new claim 57 to cover the subject matter removed from claim 35 that was dependent on claim 19.

With respect to claim 45, Applicants renew their position that inactive positive selection markers are well known in the art. Moreover, the specification provides an example of such markers at page 10, second paragraph, clause (iii).

With respect to claim 46, Applicants have split this claim into two claims, i.e., claim 46, covering previous step 46(a), and new claim 58, covering previous step 46(b).

With respect to claim 48, at a minimum the cell of claim 48 will have a structure that comprises a functional DNA sequence introduced into the Rosa26 gene by virtue of the process of claim 17.

With respect to claims 53-55, Applicants have limited to cells without prejudice.

Also, with respect to claims 53-55, Applicants have specified that the cells are "obtained" by the method of claim 17.

With respect to claims 54 and 55, neither claim recites "drug development." Instead, each method is drawn to "evaluating the effect of a drug candidate on a gene of interest," which is an aspect of drug development. And, each claim concludes with a step that specifically requires "evaluating the effect of the drug candidate on the gene of interest." In other words, each claim concludes with a step achieving the purpose stated in the preamble.

With respect to claim 55, Applicants have specified that the animal model comprises the non-human mammalian cell obtained by the method of claim 17. No reason is given and Applicants do not understand why the animal model may not comprise the non-human mammalian cell obtained by the method of claim 17.

Finally, claim 56 is again rejected, and Applicants previous arguments are simply dismissed as being "unfounded," without any explanation whatsoever why those arguments are not persuasive. Respectfully, the Examiner must provide a cogent reason why Applicants' arguments are not persuasive. The Examiner cannot simply dismiss them out of hand. The specification does, in fact, provide examples of mutually incompatiable RRSs. See, for example, the last paragraph on page 9 of the specification and the first two paragraphs on page 10.

In view of the foregoing, Applicants respectfully submit that the claims are definite. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw this rejection. An early notice that this rejection has been reconsidered and withdrawn is earnestly solicited.

Claims 17-25, 28-30, 32, 34-38, 43-46, 48 and 53-56 were rejected under 35 USC § 102(b) as being anticipated by Soprano, WO 99/53017. In response, Applicants respectfully submit that Soprano does not anticipate the instant claims.

The Examiner took the position that the instant claims were not limited to a promoter that is heterologous to the Rosa26 gene. Applicants believe the Examiner misread claim 17, but, in any event, have amended claim 17 above to make it clearer.

Applicants respectfully submit that the amendments to claim 17 make it clear that the functional DNA sequence required by main claim 17 has to be either:

(a) a gene expression cassette comprising a gene of interest operatively linked to a promoter, wherein said promoter is heterologous to the Rosa26 gene, or

(b) a DNA sequence which can be converted into such gene expression cassette.

Soriano does not describe such a construct and, therefore, cannot possibly anticipate the instant claims.

In the alternative, the Examiner finds that Soriano teaches numerous Rosa26 promoters that are heterologous to the Rosa26 locus because they are non-naturally occurring promoters. However, the customary definition of "heterologous" connotes being from a different species, not non-naturally occurring. The Examiner mentions Soriano's teachings in the paragraph bridging pages 34 and 35 as teaching Rosa26 promoters that are heterologous because they are not naturally occurring promoters. However, Applicants point out that Soriano here refers to "promoter fragments of Rosa26." Applicants respectfully submit that, consistent with the conventional definition, such promoter fragments are still Rosa26 promoters or Rosa26 derived promoters and, therefore, most certainly not a heterologous promoter as claimed in the amended claim 17.

In view of the foregoing, Applicants respectfully submit that the rejected claims are not anticipated by Soriano. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw this rejection as well. An early notice that this rejection has also been reconsidered and withdrawn is, thus, earnestly solicited.

Applicants believe that the foregoing constitutes a bona fide response to all outstanding objections and rejections.

Applicants also believe that this application is in condition for immediate allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

Early and favorable action is earnestly solicited.

Respectfully submitted,
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